Translation

PCT/DE2002/003798

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference XI 1420/02	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DE2002/003798	International filing date (*day/month/year*) 02 October 2002 (02.10.2002)	Priority date (*day/month/year*) 02 October 2001 (02.10.2001)
International Patent Classification (IPC) or national classification and IPC A61K 39/00, 39/29, C12N 15/87, 15/51, A61K 47/48, C07K 11/00		
Applicant MOLOGEN AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08 April 2003 (08.04.2003)	05 March 2004 (05.03.2004)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/DE2002/003798

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed

☒ the description:

pages 1-17, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:

pages 1-9, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the drawings:

pages 1/3-3/3, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☒ the claims, Nos. 10

☐ the drawings, sheets/fig _____

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/DE 02/03798

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	6	YES
	Claims	1-5 and 7-9	NO
Inventive step (IS)	Claims		YES
	Claims	1-9	NO
Industrial applicability (IA)	Claims	1-9	YES
	Claims		NO

2. Citations and explanations

Reference is made to the following documents:

D1: SCHIRMBECK REINHOLD ET AL: 'Priming of immune responses to hepatitis B surface antigen with minimal DNA expression constructs modified with a nuclear localization signal peptide', JOURNAL OF MOLECULAR MEDICINE (BERLIN), vol. 79, nos. 5-6, June 2001 (2001-06), pages 343-350, cited in the application

D2: MCCLUSKIE M J ET AL: 'ROUTE AND METHOD OF DELIVERY OF DNA VACCINE INFLUENCE IMMUNE RESPONSES IN MICE AND NON-HUMAN PRIMATES', MOLECULAR MEDICINE, BLACKWELL SCIENCE, CAMBRIDGE, MA, US, vol. 5, no. 5, May 1999 (1999-05), pages 287-300

D3: EP-A-0 941 318 (SOFT GENE GMBH) 15 September 1999 (1999-09-15).

Unless indicated otherwise, the present report relates to the passages cited in the international search report.

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1. **Amendments (PCT Article 19(2))**

The applicant submitted an amended set of claims with the letters of 27 November 2003 and 5 December 2003. The amended claim 1 fails to meet the requirements of PCT Article 19 (2) in so far as the originally filed application does not disclose that the expression construct of the invention must contain sequences which code for a plurality of antigens, in order to accomplish the desired function, namely to generate a type 1 cell-mediated immune response. Therefore, for the purpose of establishing the present report, the replacement of the wording "one or more antigens" by the expression "a plurality of antigens" has been disregarded.

2. **Novelty (PCT Article 33(2))**

According to the present wording (see also point 4.1 of the present report), the subject matter of the amended claims 1-5 is not novel. As the applicant correctly observes in his reply, said claims are directed to the use of a substance for producing a vaccine. However, said substance and the use thereof for producing a vaccine have already been disclosed in D1. Thus, D1 describes a minimalistic immunologically defined gene expression vector (MIDGE) consisting of covalently closed linear DNA molecules with a linear double-strand region, wherein the single strands forming the double strands are linked by short single-strand loops of DNA and consist only of the antigen-coding sequence under the control of an operable promoter

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in the animal to be vaccinated and a terminator sequence. Said vector is covalently linked with the nuclear localisation peptide of SV40 and codes for the small surface antigen of hepatitis B (hepatitis B small surface antigen HBsAG). In addition, D1 describes the use of the vector for the production of a vaccine (page 346, left-hand column, third paragraph).

The applicant has argued that according to the present application, in contrast to D1, following intradermal **injection** instead of intradermal administration using a gene canon, the aforementioned DNA expression product induces a Th1 cell-mediated immune response. However, the discovery of an **action mechanism** of a substance (in this case, the induction of a Th1 cell-mediated immune response following intradermal injection) cannot be considered a **therapeutic application** *per se* but requires, in addition, a practical application in the form of an actual, defined treatment of a pathological disease in order to constitute a definable contribution to the art. Even the fact that the DNA gene expression product is injected intradermally and not intramuscularly is insufficient on its own for establishing novelty over the prior art, since it is not clear to what extent the modified form of administration changes the method for producing the claimed vaccine.

2.2 The amended claims 7-9, likewise, lack novelty over D1. Said claims are drafted as claims directed

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to the first medical use of the DNA expression construct mentioned in the amended claims 1-6. The DNA expression construct to which the amended claims 1-5 relate and the medical use thereof have already been disclosed in D1, which describes the use of said DNA expression construct for inducing a type 1 cell-mediated immune response following intramuscular injection and a type 2 humoral immune response following intradermal administration of particle-bound DNA using a gene canon.

3. **Inventive step (PCT Article 33(3))**

The amended claim 6 fails to meet the requirements of PCT Article 33(3). The subject matter of said claim differs from the disclosures of D1 in that the oligopeptide bound to the DNA expression construct for increasing the efficiency of transfection contains the nuclear localisation sequence of HIV instead of the nuclear localisation sequence of SV40. The problem solved by the present claim is therefore that of devising an alternative DNA expression product for use in the production of a vaccine.

However, since the nuclear localisation sequence of HIV and the use thereof in MIDGE vectors for increasing the efficiency of transfection already belonged to the prior art (D3) before the priority date of the application, substituting the nuclear localisation signal of HIV for that of SV40 cannot be regarded as inventive.

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4. Further objections

4.1 In their current form, claims 1-6 lack clarity; it is unclear at present whether they claim only the use of the aforementioned product for making a vaccine (which does not appear to be novel in the case of claims 1-5; see point V.2.2.1 of this report) or whether, in addition, they claim the use thereof for producing a vaccine which is then used for immunisation against specific diseases. According to the present wording, the therapeutic use of the DNA expression construct is defined only in functional terms, as an action mechanism, which does not allow of any practical application in the form of a defined, specific treatment of a pathological disorder (a disease).

In consequence, claims 1-6 in their current form cannot be regarded as claims that are directed to the second medical use of a product.

4.2 In addition, the amended claim 2 and claims 4-9 contain erroneous back-references.